ACAAI 2013
Workshop W-25
Update on Urticaria and Angioedema

November 10, 2013
3:30-5:30 Pm

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Disclosures

Dr. Saini

- Research Interests-NIH, Genentech, Novartis
- Other Interests
  - Consultant to Array, Genentech, Medimmune, Novartis, Pharmacyclics, Kendle, Regeneron
- Organizational interests: AAAAI, *UptoDate, Journal of Investigative Dermatology*

Dr. Dreskin

- Research Interests-NIH, Genentech, AAAAI
- Other Interests
  - Consultant, Clinical Immunization and Safety Assessment (CISA) Network (administered by Vanderbilt University)
  - Medical Expert Panel, Division of Vaccine Injury Compensation (DVIC), Department of Health and Human Services
  - Member, Medical Expert Panel: Vaccine Review, Pfizer, Inc.
- Organizational interests: AAAAI

Overall Learning Objectives

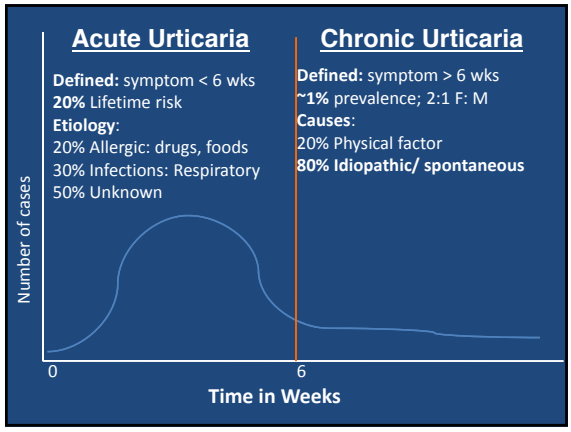
I. Review the pathophysiology of chronic spontaneous/idiopathic urticaria and angioedema - Saini
II. Review the differential diagnosis of angioedema without urticaria- Dreskin
III. Discuss the evaluation of patients with urticaria and angioedema – Saini and then Dreskin
IV. Review the side effects of immunomodulatory agents - Dreskin
V. Review the new therapeutic modalities for refractory chronic idiopathic/spontaneous urticaria and angioedema - Saini

I. Pathophysiology of chronic spontaneous/idiopathic urticaria and angioedema

Urticaria: Overview

- Lifetime risk of 20-25%
- Itch is major symptom
- Range: mild and self-limited to severe disease for yrs
- Multiple factors linked to urticaria disease
  - Infections: trigger innate immune response
  - Allergens (drugs, foods): specific IgE, acquired immunity
  - Inducible by physical stimulus- cold or heat exposure
  - Idiopathic/Spontaneous: autoimmune basis?
- Classification of disease by time course or by etiology

Grattan, Clin Medicine 2012; Kaplan, NEJM 2002



Subsets of Chronic Urticaria

Physical Urticaria-20%

- stimulus activates skin mast cell
- Subsets (freq %) :
  - Pressure/Dermographism -36%
  - Temp/Cholinergic-34%
  - Cold-induced-13%
  - Delayed pressure-11%

Idiopathic urticaria-80% (Spontaneous)

Urticaria **Angioedema**

Urticaria & Angioedema

Chronic Idiopathic/Spontaneous Urticaria (CIU/CSU):

Features:

- Thyroid disease- 2X the freq in general population
- QOL impairment like coronary artery disease
- Economic: >$2000/yr for moderate patient

Treatment:

- H1, H2, Leukotriene, steroids, CSA, immune agents

Prognosis:

- ~50% of urticaria cases clear by 1 year
- ~20% have symptoms more than 5 years
- Angioedema predicts severe disease

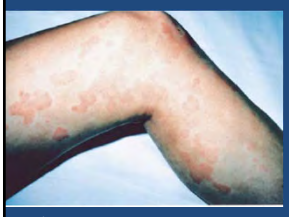
Cooper et al, J Am Acad Derm 1991, Kulp-Shorten Rheum Dis Clin 1996, Champion Br J Derm 1969, Toubi et al, Allergy 2004, Kaplan NEJM, Delong JAAD 2008

CIU: Skin Lesion Pathology

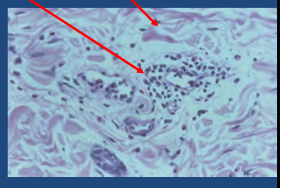
Perivascular lymphocytic infiltrate

Interstitial edema

Lesional Skin



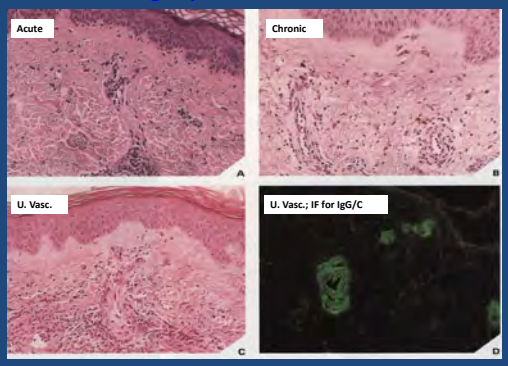
Kaplan, NEJM 2002



Grattan et al, J Am Acad Dermatol 2002

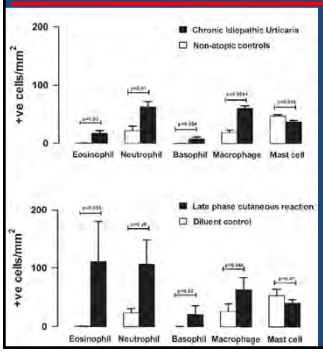
- Individual lesions < 24 hrs
- Lack epithelial change on biopsy

Histologic Spectrum of Urticaria



Fireman and Savin, Atlas of Allergies, 2nd ed., 1996

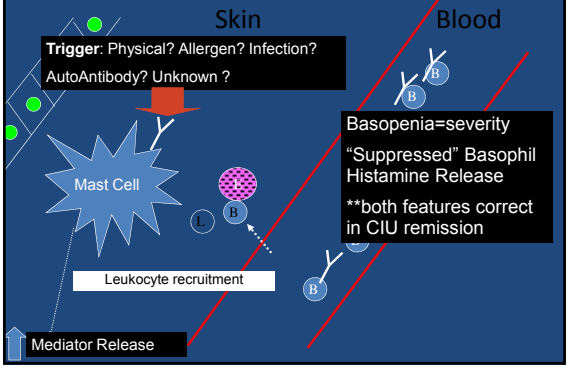
Leukocyte infiltrate in skin biopsies of CIU is similar to allergen-late phase



- Most common is CD4+ T cell
- Profiles is **TH1 &TH2** in CU vs. **TH2** in allergen late phase
- Basophils seen in both
- Mast cell activation in both

Ying, JACI,2002

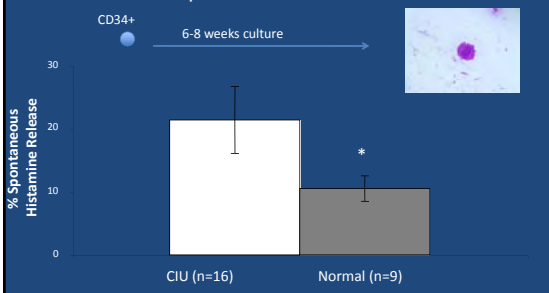
CIU/CSU : Proposed pathophysiology



Skin Mast Cells in CIU

- Skin mast cell release to 48/80 in active CIU is increased versus remission: reversible skin mast cell hyper-responsiveness
  - Jacques et al, J Allergy Clin Immunol 1992
- Mast cell number not increased in biopsies
  - Smith et al, J Allergy Clin Immunol 1995
- Serum tryptase not elevated in CIU patients
  - Schwartz J Clin Invest 1995
- Serum tryptase is higher in CIU vs atopics
  - 6. 6 ng/ml CU vs. 4.4 normals vs 4.5 atopic
  - Ferrer Clin Exp Allergy, 2010

Culture-derived HMCs from CIU pts have increased Spontaneous Histamine Release



Supports inherent hyper-reactivity of MC progenitors of CIU subjects

Saini, Clin Immunol, 2009

Basophils: Roles in Chronic Urticaria

ACTIVE CIU DISEASE:

- Blood basopenia with normal bone marrow numbers
- Basophils show FcεRI-mediated HR suppression
- Basopenia is related to disease severity symptoms
- Basophils are present in skin lesions (BB1 stains)

REMISSION:

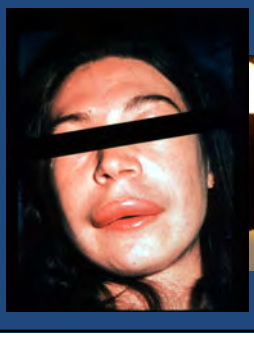
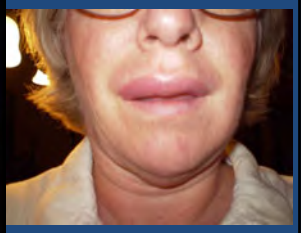
- Blood basophil number and FcεRI-mediated HR rise

THERAPY:

- Basophil migration and mediators inhibited by steroids
- Rising blood basophil number and FcεRI-mediated response rise seen with omalizumab

Rorsman 1961; Greaves 1974; Kern 1976; Grattan 2001, 2003; Sabroe 1998; Ying 2002; Vonakis, 2007 ; Caproni ,2005; Eckman, 2008

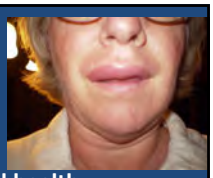
II. Differential diagnosis of angioedema without urticaria

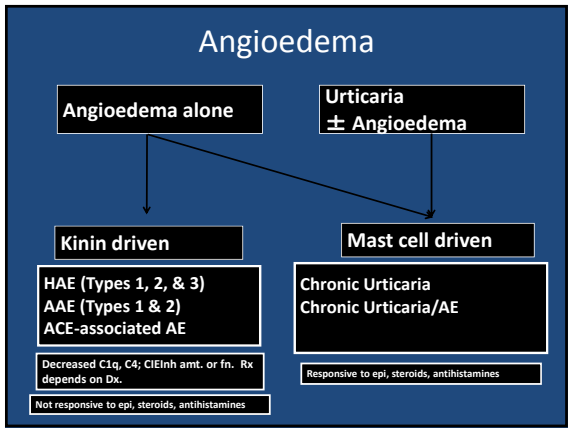
Case #1

- 33 yo woman generally in good health
  - Has had episodic swelling of the face and/or extremities since adolescence
    - Brought on by mild trauma but also begins spontaneously
  - No airway compromise
  - Family history: Mother and Maternal grandfather both had similar histories

Case #2



- 52 yo woman generally in good health
  - Has had episodic swelling of the face for the last 3 months
    - May be related to foods but difficult to pin down
    - No hives or flushing
    - No airway compromise
  - No airway compromise
  - Family history: negative



Case #3

- 48 yo woman with DM, HTN, and ESRD, s/p kidney/pancreas transplant
- April, 2013 reported to PCP a single episode of lip swelling ~1 month prior after eating catfish.
- No further ingestion of catfish and no further episodes of lip swelling
- Had been on lisinopril for 8 months
- PCP desired to have the renal protection of the ACE I
- Was advised by PCP to continue to avoid catfish

Case #3

- 3 months prior to diagnosis
  - ED visit with bowel obstruction
  - Resolves spontaneously
- 2 months prior to diagnosis
  - Primary care visit
  - Different provider
  - Lip swelling attributed to canteloupe

Case #3

- Ultimately, the patient had a severe episode of swelling not related to eating catfish or canteloupe
  - Airway compromise with intubation
  - Does well
- Take home lessons:
  - ACE induced AE can occur long after the drug was started
  - All AE is intermittent
  - Etiology is difficult to establish, especially by history
  - ARBs are just as good as ACE Is with less risk

Hereditary Angioedema

- Recurrent self-limited but potentially life threatening attacks of angioedema
  - Skin, Upper airway, GI
  - Very important consideration in ED
- Triggers
  - Trauma, strong emotions, spontaneous
- Duration
  - Hours to days
- No urticaria or pruritis

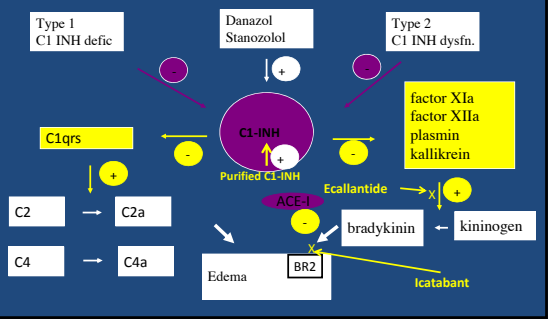
Hereditary Angioedema

- Autosomal dominant with incomplete penetrance. Spontaneous mutations in 25%
- HAE I
  - Low levels of C1 esterase inhibitor
- HAE II
  - Dysfunctional C1 INH
- Both HAE I and HAE II
  - Diminished C4 between attacks
  - Very low C4 during attacks
- HAE III
  - Normal C4 and C1 INH level and function
  - Still being defined. Probably rare.

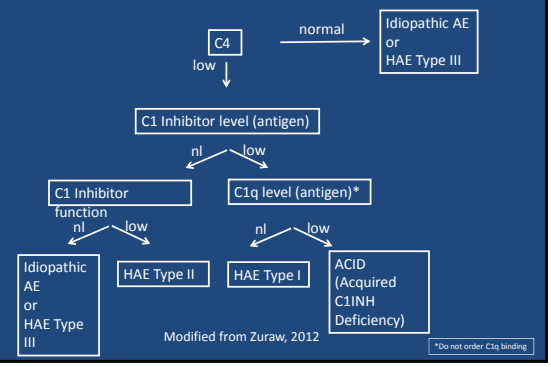
Acquired Angioedema

- Rare; Onset > 50 yo; neg. fam. Hx.
- AAE, type I
  - Lymphoproliferative disorder
  - Monoclonal gamopathy, lymphoma,
- AAE, type II
  - Autoantibodies to CI-INH
- Low C1q levels in addition to depletion of C4 and C2.

C1 Esterase Inhibitor (C1-INH) Deficiency and Angioedema



Diagnostic Algorithm for AE not due to foods or drugs and poorly responsive to anti-histamines, corticosteroids, and/or epinephrine



III. Evaluation of patients with urticaria and angioedema

Diagnostic Approach to CU

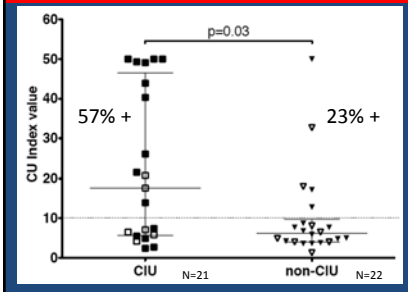
History and Physical Exam:

- Duration of episodes and lesions appearance (photos)
- Medication/food history
- Identify physical triggers (~20%)- heat, cold, pressure, sunlight
- Consider infections

Possible Lab studies:

- Basic series: CBC, BMP, LFTs, Urinalysis
- Other testing guided by physical exam or history
- Extended: WESR, anti-thyroid antibodies,TSH, C3, C4
- "Autoimmune" tests- ASST, Basophil CD203c or CIU index?
- Skin biopsy to exclude vasculitis or define cellular influx in atypical cases: prolonged lesion duration, pigment changes, epithelial changes

"Positive" HRA (CU Index) occurs in non-CIU patients serum



Filled symbols indicate positive IgG anti-FcεRIα

or positive IgG anti-IgE by IEMA

Eckman et al., J Invest Derm 2009

Positive CIU Index in SLE/CIU/ Normals

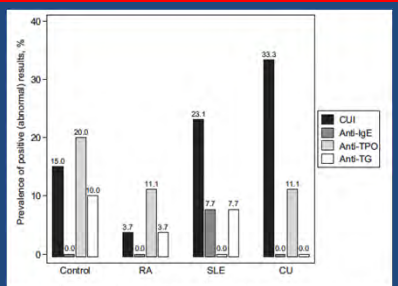


Figure 1. Prevalence of a positive (abnormal) result by disease status. CU indicates chronic idiopathic urticaria; CUI, CU Index; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TG, thyroglobulin; TPO, thyroid peroxidase.

C.B. Cho et al. / Ann Allergy Asthma Immunol 110 (2013) 29–33

Approach to Chronic Urticaria: Idiopathic/Spontaneous

Non sedating H1-Antihistamine (nsAH)

If symptoms persist after **2 weeks**

nsAH updosing

If symptoms persist after **2 weeks**

+H2 antagonist, + Leukotriene antagonist, change nsAH, supplement with sAH

Exacerbation: Systemic Steroid (for 3-7 days)

Consider skin biopsy

If symptoms persist after **1-4 weeks**

****Refractory CU**

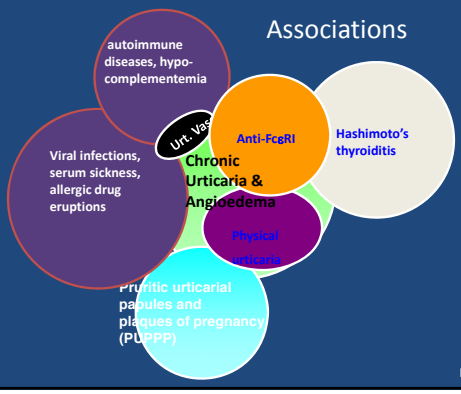
Sulfasalazine,Cyclosporine A, Omalizumab

Exacerbation: Systemic Steroid (for 3-7 days)

Low dose daily steroid with gradual taper

Modified from EAACI/GA(2)LEN/EDF/WAO Urticaria Guidelines- Zuberbier *Allergy* 2009

Associations



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Beyond antihistamines: Treatment of Specific Conditions

- Euthyroid CIU with anti-thyroid antibodies
  - Controversial
- H. *pylori* positive patients
  - Not generally accepted
  - Need to demonstrate irradication
- Neutrophil predominant CU
  - Evolving concept
- Food allergies
  - Rare but not absent
  - Demonstration of negative skin tests for foods has value (with minimal risk) for selected patients

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Thyroid autoimmunity

- Thyroid antibodies
  - Increased (>2-fold) in euthyroid patients with CIU
    - Leznoff et al. Arch Derm 119;636-640, 1983
- Case Studies of treatment with l-thyroxine
  - Resolution/recurrence in CIU patients on/off l-thyroxine
    - Rumbyrt et al JACI 96:901-905, 1995
- Small randomized trial (n=15); no effect at 12 wks
    - Kiyici S eta l Clin Exp Dermatol 2010; 35:603-7

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Treatment of H. *pylori*

- Antibodies to H. pylori
  - Meta analysis -10 studies with 274 CU subjects
    - Eradication of *H. pylori* assoc with remission of urticaria
    - OR=2.9 (1.4-6.8; p=0.005) c/w *H. pylori* positive without eradication
    - OR=4.7 (2.6-17.6; p<0.001) c/w *H.pylori* negative
    - Federman et al J Am Acad Derm 49:861-864, 2003
  - Epi-phenomena v. pathogenic?
  - Opinion: reasonable to test and treat

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Neutrophil Predominant Urticaria

- Approx 10% of patients with severe CU have a predominant neutrophil infiltrate
- Possible mild manifestation of urticarial vasculitis
- Recommendation: drugs with anti-neutrophil activity
  - Colchicine
  - Dapsone

Dreskin

IV. Use and side effects of Immunomodulatory Agents for Chronic Spontaneous Urticaria

The Tried and True:
The $20 Cure for Urticaria

- An index card with
  - the telephone number of a local taxi cab company
  - the name and address of your nearest competitor
- A $20 bill

The Tried and True: Antihistamines for Urticaria

- Anti-histamines are better than placebo
  - Multiple trials with multiple anti-histamines
- Minimally sedating or non-sedating H1 blockers
  - Differences amongst these - difficult to demonstrate
  - Cetirizine and levocetirizine may be better at bedtime
- Doses often used in excess of FDA approval
  - Increased cetirizine more effective in DPU and cholinergic urticaria
    - Reviewed in Zuberbier and Maurer, Acta Derm Venereol 87:196-205, 2007
  - Increased fexofenadine without extra effect on CIU
    - Nelson et al. Annals of Allergy, Asthma, & Immun 84(5):517-22, 2000

The Tried and True: Antihistamines for CU

- Non-sedating antihistamines preferable
- Diphenhydramine or hydroxyzine as supplements
- Cholinergic urticaria- High dose hydroxyzine
- Doxepin - most potent H_1 and H_2 blocker
  - Start at 10mg QHS and advance slowly
  - Dry mouth and weight gain are prominent
- Antihistamine toxicity is rare
- H_2 blockers
  - Ranitidine or famotidine >> cimetidine 2/2 fewer drug interactions

CIU: Beyond antihistamines

- Eicosinoid Pathway
  - Leukotriene pathway mediators
  - COX-2 inhibitors
  - PAF inhibitors
- Anti-Inflammatory
  - Corticosteroids
  - Hydroxychloroquine
  - Sulfasalazine
  - Colchicine
  - Dapsone
- Immunomodulatory
  - Cyclosporine
  - Mycophenolate
  - Omalizumab(anti-IgE)
  - IVIg
- Anti-metabolites
  - Methotrexate
  - Cyclophosphamide

Indicators of refractory CIU/CSU

- Lack of control with H1 antagonists ~ 50%[1]
- Longer disease duration[2]
  - 50% have disease > 1 yr; ~20% >5 years
  - Angioedema associated with longer disease
- ASST+ may predicts disease duration/severity[3]
  - Medication needs- Review of 236 university cases 28% required cyclosporine or prednisone[4]
- *Overall: 20%-50% are refractory disease defined by poor H1 response, oral steroid requiring, persistant disease*
- *No biomarker (cellular or serologic) of refractory cases*

[1]Humphreys 1998, Nettis 2003, Potter 2009; [2] Kozel 2001, Toubi 2004; [3] Vohra 2011 Belot 2010; [4] Najib 2009

Rationale for Cyclosporine (CSA) in CU

Skin disease with recruitment of lymphocytes expressing Th1, Th2 cytokines

- *CSA suppresses T cell activation, cytokine release*

Enhanced MC degranulation (Jaques 1992) & altered basophil degranulation (Vonakis & Saini 2008)

- *CSA inhibits IgE receptor-mediated release of:*
  - *Histamine, lipid mediators and cytokines by basophils and skin mast cells* (Pedersen 1985, Marone 1988, Stellato, 1992, Harrison 2007)

CSA in H1 resistant CU- case reports 1990's

- 6 mg/kg in 3 pts, stopped due to side effects (SE)[1]
  - Headache, blood pressure, renal function
  - Results seen in 1 week
- 3 mg/kg x 4 wks in 12 pts[2]
  - safe and effective
- *Modified*- 3 mg/Kg 6 wks +1-2mg/kg 6 wks=3 mos[3]
  - N=25, **25% dropped** (2-SE, 4-no response); Open-label
  - 19 followed for 6 months, **10% had SE**
  - Rapid symptom relief by 1 week
  - 68% (13/19) remission at 3 mos , 58% (11/19) at 6 mos
  - **ASST + did not predict clinical response to CsA**

[1] Frandin 1991; [2] Barlow 1993; [3] Toubi 1997

Randomized, double-blind, placebo controlled trials of CSA in resistant CU-2000's

- CSA 4 mg/Kg x 4 wks in ASST+, N=30[1]
  - Initial 4 wks: 42%(8/19) CSA, 0/10 placebo responded
    - ***6 of 8 CSA responders relapsed by 6 wks off CsA***
  - *Non-responders (7 CSA/10 pla) given CSA 4 wks*
    - *11/17 responded*
  - **Overall :19/29 (65%) responded to CSA**
    - 5/19 (26%) remained sx-free at 20 wks
  - **SE's in >40%**: GI, HA, paresthesia; dose reduced in 4
- RDBRPC,16 wks vs. 8 wks of CSA, n=99 [2]
  - CsA 5-4 mg/kg x 4 wks, then 3 mg/kg (4 or 12 wks) + cetirizine
  - **63% response at 8 wks**, no sign differ at 16 wks
  - **SE in 60%** : GI, paresthesias, infections most common

[1]Grattan 2000; [2] Vena 2006

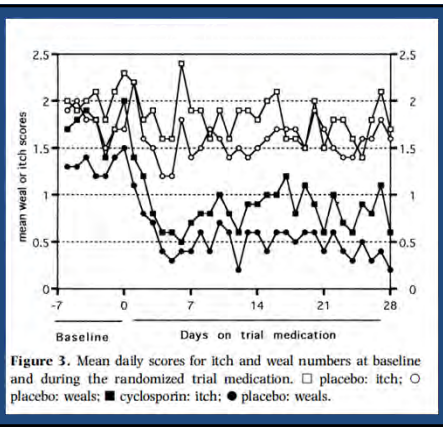
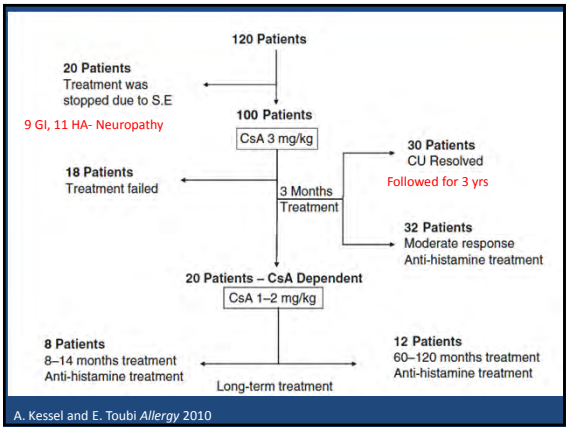


Figure 3. Mean daily scores for itch and weal numbers at baseline and during the randomized trial medication. □ placebo: itch; ○ placebo: weals; ■ cyclosporin: itch; ● placebo: weals.

Cyclosporine A in Severe Urticaria
A. Kessel and E. Toubi *Allergy* 2010

- Series of 120 severe CU pts, non-responders to H1, H2, with QOL disturbance
- Start 3 mg/kg, if response at 2 mos, taper to off in 1 month (2mg/kg then 1mg/kg)
- If sx's recur with taper, stay on 1-1.5 mg/kg
- Monitor every 4-6 wks for symptoms
- BP, CBC, electrolytes, Cr, q 6-8 wks then every 3 months



A. Kessel and E. Toubi *Allergy* 2010

Summary: Use of CSA in Refractory CU

Benefits:
- Fast onset of relief (~1 wk)
- Effects on multiple cells types (T cells, MCs, Basophils)
- Rebound with short term treatment~1 month
- 35-40% fail to respond or have intolerance
- 30% long-term disease benefit, 30% reduction in sx's
- CSA (1-1.5 mg) may be useful longer term management

Risks:
- Side effects >10 %: GI, HA, paresthesias
- HTN and nephrotoxicity
  - Monitor blood pressure and renal function regularly
- Malignancy risk unclear based on transplant data?

Clinical Pearls for use of CSA

- Document discussion of potential side effects and black box warning (late lymphomas)
- Two methods of birth control when applicable
- Use "modified" CSA
- Start at 3 mg/kg/day in divided doses
- Check creatinine and BP monthly for 3 months and then Q3 months
  - Consider obtaining trough levels of CSA
- Those with underlying hypertension are at greatest risk
- Calcium channel blockers are the anti-hypertensive agent of choice
- Limit prescriptions to last until the next appointment
  - No refills

Other Immune agents in refractory CIU/CSU

Agent	Evidence /side effects	Cost
Corticosteroids	Low /High	Low
Dapsone	Low/Moderate	Low
Sulfasalazine	Low/Moderate	Low
Intravenous IgG	Low/Moderate	High
Mycophenylate	Low/Moderate	High
Hydroxychloroquine	Low/Low	Low
Cyclosporine	Moderate/High	High
Omalizumab	Excellent/Low	Higher

Khan DA. In: Maibach HI, Gorouhi F ed. Evidence Based Dermatology 2nd ed. 2011

Clinical Pearls for other immunomodulatory agents

- Obtain control prior to adding a new agent
- Dapsone
  - Check G6PD level
  - CMP and CBC monthly X 3 & then Q3monthly
- Sulfasalazine
  - CMP and CBC monthly X 3 & then Q3monthly
  - Add folic acid if >1 month
  - Sun sensitizer
- Mycophenylate
  - Two methods of birth control
- Hydroxychloroquine
  - Slit lamp exam @ 6 months
  - Opthamologist, not Optician or Optometrist
- IVIg
  - Risk of biologics
  - Risk of serum sickness

Skin infiltrate-based treatment options

Neutrophil-predominant urticaria

- **Colchicine**
- ***Dapsone**: 25-100 mg qD (G-6-PD)
  - J Dermatolog Treat. 2008;19(2):92-6

Lymphocyte-eosinophil urticaria

- ***Sulfasalazine**: 500 mg qD to 4 gms qD
  - McGirt, Arch Dermatol, 2006

*Require lab monitoring (CBC, LFTs)

Efficacy & Safety of Sulfasalazine-JHU

- 31 pts treated between 2007-2012
- 61% female, Median age= 45 yrs
- 65% on ≥ 3 medications for urticaria
- 32% on steroids >1 mo pre-sulfa
- Disease duration median of 19 months
- 71% had angioedema
- 24 had bx, 19 lymphocyte predominant

Anthony Orden et al, ACAAI, 2013

Outcome of safety labs

TABLE 2. Frequency of Clinical Efficacy Measures

		n=	%
1A:	Abnormal CBC leading to dose change	6	1.9%
1B:	Abnormal LFT leading to dose change	1	0.3%
2:	Abnormal CBC & LFT no dose change	0	0.0%
3A:	Abnormal CBC no dose change	112	36.0%
3B:	Abnormal LFT no dose change	13	4.2%
4:	No CBC or LFT abnormality	179	57.6%
Total Number of Lab Draws		311	100.0%

1A –drop in WBC or H/H
1B – max LFT abnormality was 3 fold ULN

Efficacy & Safety of Sulfasalazine-JHAAC

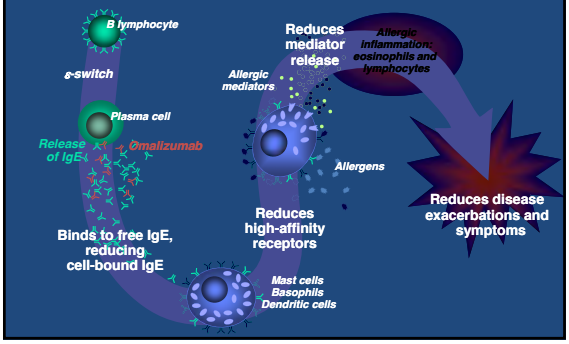
- Median treatment was 64 wks
  - 4.4 wks to reach 2,000mg
- 84% (n=26) improved at 3 months
- 32%/52% (n=16) asym by 3/6 months
- 35% (n=11) remained asym off sulfa
  - Total 38 of 68 wks tx at full dose
  - 7 on steroids, f/u is 70 wks off therapy
- 9/10 on steroids weaned (1 adrenal insuff)
- Average med regimen reduced by 50%

Recommendations regarding immunomodulatory agents

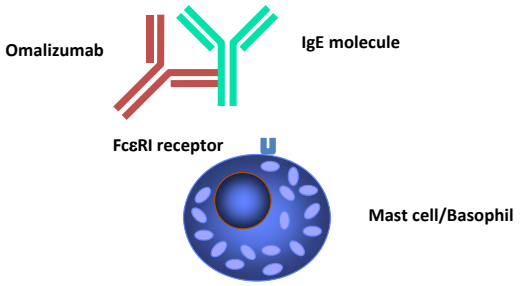
- Determine patient needs
  - Minimal bother
    - HCQ (200 mg BID)
  - Severe aggravation
    - As below
  - Risk adverse
    - Discuss the risks of corticosteroids
    - HCQ
- Skin biopsy
    - Colchicine (0.6 mg BID) v Dapsone (100 mg daily)
    - Sulfasalazine (start at 500-1,000 mg BID)
    - HCQ + sulfasalazine
- Risk adverse
    - HCQ, perhaps at higher doses
    - Omalizumab if available
- Sulfa allergic with lymphocyte/eosinophils on BX or failed Sulfasalazine and less risk-adverse
    - HCQ
    - CSA (start at 3 mg/kg/day)
    - Mycophenylate
    - Omalizumab

V. Review data regarding omalizumab, a new therapeutic modality for refractory chronic idiopathic/spontaneous urticaria and angioedema

Omalizumab: Mechanisms of Action in Allergic Disease

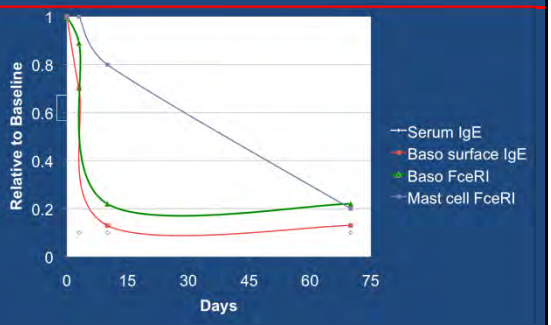


IgG Anti-IgE (Omalizumab) Blocks IgE Binding to Mast Cells and Basophils



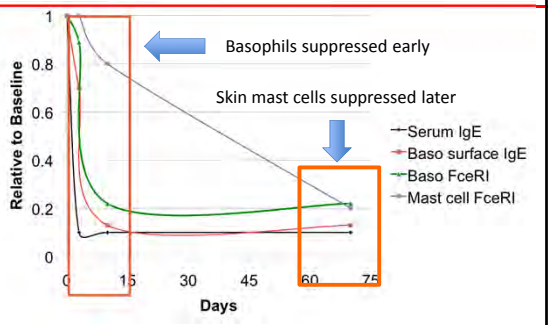
> 90% fall in surface IgE & FceRI on both cells

Timing of Omalizumab Effect on IgE, Blood Basophils, Skin Mast Cells



Beck et al, JACI 2004, Ong et al JACI 2005 Eckman et al JACI, 2010

Timing of Omalizumab Effect on IgE, Blood Basophils, Skin Mast Cells



Rationale for omalizumab in CIU

***Evidence shows*:**

1) MC activation with late-phase infiltrate in skin

2) Basophils altered FcεRI HR, recruited to skin lesions, basopenia related to disease severity

In theory, omalizumab in CIU disease can:

- Alter basophil and MC FcεRI functions
- Differentiate MC & basophil roles based on the onset of action
- Reduce targets for autoantibodies (IgE & FcεRIα)?

Omalizumab Therapy in CIU

- Randomized, double-blind study examining the addition of omalizumab or placebo in 20 subjects with active CIU despite standard therapy

Inclusion Criteria:

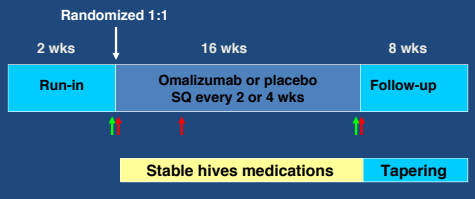
- Ages 18 to 80
- Symptoms for 12 wks
- Angioedema
- Daily H1 blocker
- High itch score: 2 out of 3
- Total IgE: 10-700 IU/mL

Exclusion Criteria:

Systemic corticosteroids
immunosuppressants
<1 mo prior to enrolling

L.M. Gober, P.M. Sterba, J.A. Eckman, S.S. Saini. AAAAI 2008

Omalizumab in CIU: Randomized, Double-blind,placebo-controlled trial

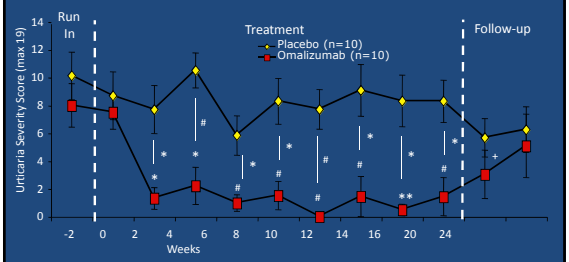


↑ Skin bx

↑ Blood -IgE & basophil studies

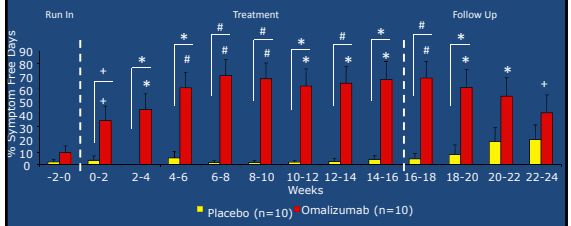
⁎ Clinical Outcome Measures every 2 weeks

Physician-Assessed Urticaria Severity Score



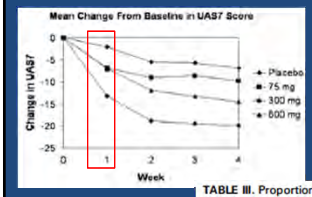
+p<0.05 ,* p<0.01, # p<0.001,** p<0.0001

Patient Reported Symptom-Free Days



+p<0.05 ,* p<0.01, # p<0.001,** p<0.0001

Phase II-single dose study of omalizumab in H1 resistant CU



- Multi-site, single dose
- Symptom reduced 1 wk
- Dose effect of drug

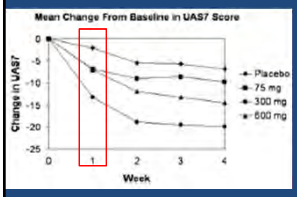
TABLE III. Proportion of patients with 50% or greater improvement from baseline in UAS7 at week 4

No. (%) of patients with improvement	Placebo (n = 21)	OMA, 75 mg (n = 23)	OMA, 300 mg (n = 25)	OMA, 600 mg (n = 20)
100% Improvement	0 (0.0)	1 (4.4)	9 (36.0)	6 (28.6)
90% Improvement	1 (4.8)	1 (4.4)	10 (40.0)	6 (28.6)
75% Improvement	2 (9.5)	5 (21.7)	15 (60.0)	7 (33.3)
50% Improvement	5 (23.8)	12 (52.2)	20 (80.0)	12 (57.1)

OMA, Omalizumab.

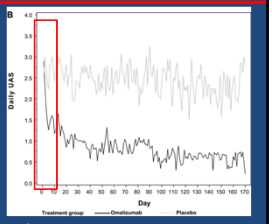
Saini et al, JACI 2011

Phase II studies of omalizumab in H1 resistant CU show rapid sx response



- Multi-site, RDBPC n=90
- Single dose, not IgE based
- No selection for autoimmune features
- Symptom reduced 1 wk

Saini et al, JACI 2011



- Multi-site, RDBPC n=42
- Asthma dosing
- Pts with IgE-thyroperoxidase
- Symptom reduced 1 wk

Maurer et al, JACI 2011

Original Article

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

N Engl J Med
Volume 368(10):924-935
March 7, 2013

The NEW ENGLAND JOURNAL of MEDICINE

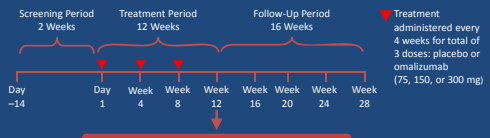
Study Overview

Objective	**Evaluate the efficacy and safety of omalizumab compared with placebo in patients with moderate-to-severe refractory CIU despite receiving concomitant H_1-antihistamine therapy**
Design	Phase III, global, multicenter, 1:1:1:1 randomized, double-blind, placebo-controlled trial
Population	Patients (12–75 years) with CIU who remain symptomatic on H_1-antihistamine treatment
Sample Size	323 in US and Europe
Primary Efficacy Endpoint	Change from baseline in weekly ISS at Week 12
Key Secondary Endpoints (all at Week 12)	– Change from baseline in weekly number of hives score – Proportion of patients with weekly UAS7 ≤6 – Change from baseline in overall DLQI – Proportion of angioedema-free days from Week 4 to Week 12
Post-hoc analysis	– Proportion of patients with UAS7=0 at Week 12

DLQI=Dermatology Qualify of Life Index; ISS=Itch-Severity Score; UAS7=weekly urticaria activity score

SS1

Study Design – Asteria II



Week 12: primary endpoint assessment

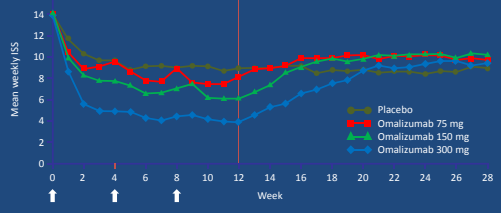
Patients on stable dose of H1 antihistamine throughout treatment period and were permitted rescue DPH 25 mg up to 3/day

N= 323

ISS1

Mean Weekly Itch-Severity Score

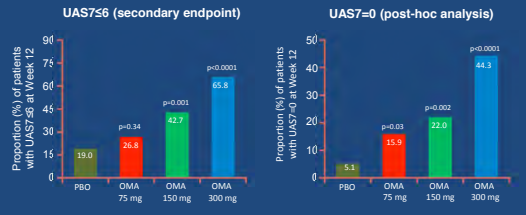
- Rapid onset of treatment effect
- Clear dose-response relationship observed
- Mean weekly ISS increased towards baseline after Week12



ISS=itch-Severity Score; mITT=modified intention-to-treat population

Responder Analysis

- Significantly higher proportion of patients in the omalizumab 150 mg and 300 mg groups had symptoms which were well controlled (UAS7≤6) vs. placebo
- A large proportion of patients treated with omalizumab 300 mg were completely symptom free (UAS7=0) by Week 12



mITT=modified intention-to-treat population; OMA=omalizumab; PBO=placebo; UAS7=weekly urticaria activity score

Summary: Trials of omalizumab in CIU

Benefits:

- Rapid symptom reduction (1 wk in Phase II, III)
  - Faster than skin MC IgE receptors fall (8-10 wks)
  - Symptom relief is timed to drop in Free IgE and changes in basophil receptors
- Benefits both CIU & autoimmune CU (Kaplan 2008, Maurer 2011)
- Phase III studies completed (Phase IIIs)
  - Benefits in refractory patients on standard H1
  - Benefits seen in pts on updosed H1-4x, H2, ± LTRA (Kaplan 2013)

Novel role for IgE actions on Basos/MCs in CU

Acknowledgements

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